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\* \* \* \* \* Welcome to STN International \* \* \* \* \*

|              |  |        |  |
|--------------|--|--------|--|
| NEWS         | 1  |        | Web Page URLs for STN Seminar Schedule - N. America                                      |
| NEWS         | 2  |        | "Ask CAS" for self-help around the clock   |
| NEWS         | 3  | OCT 23 | The Derwent World Patents Index suite of databases on STN has been enhanced and reloaded |
| NEWS         | 4  | OCT 30 | CHEMLIST enhanced with new search and display field                                      |
| NEWS         | 5  | NOV 03 | JAPIO enhanced with IPC 8 features and functionality                                     |
| NEWS         | 6  | NOV 10 | CA/CAPLUS F-Term thesaurus enhanced  |
| NEWS         | 7  | NOV 10 | STN Express with Discover! free maintenance release Version 8.01c now available          |
| NEWS         | 8  | NOV 20 | CAS Registry Number crossover limit increased to 300,000 in additional databases         |
| NEWS         | 9  | NOV 20 | CA/CAPLUS to MARPAT accession number crossover limit increased to 50,000                 |
| NEWS         | 10   | DEC 01 | CAS REGISTRY updated with new ambiguity codes  |
| NEWS         | 11   | DEC 11 | CAS REGISTRY chemical nomenclature enhanced  |
| NEWS         | 12   | DEC 14 | WPIDS/WPINDEX/WPIX manual codes updated  |
| NEWS         | 13   | DEC 14 | GBFULL and FRFULL enhanced with IPC 8 features and functionality                         |
| NEWS         | 14   | DEC 18 | CA/CAPLUS pre-1967 chemical substance index entries enhanced with preparation role       |
| NEWS         | 15   | DEC 18 | CA/CAPLUS patent kind codes updated  |
| NEWS         | 16   | DEC 18 | MARPAT to CA/CAPLUS accession number crossover limit increased to 50,000                 |
| NEWS         | 17   | DEC 18 | MEDLINE updated in preparation for 2007 reload   |
| NEWS         | 18   | DEC 27 | CA/CAPLUS enhanced with more pre-1907 records  |
| NEWS         | 19   | JAN 08 | CHEMLIST enhanced with New Zealand Inventory of Chemicals                                |
| NEWS         | 20   | JAN 16 | CA/CAPLUS Company Name Thesaurus enhanced and reloaded                                   |
| NEWS         | 21   | JAN 16 | IPC version 2007.01 thesaurus available on STN   |
| NEWS         | 22   | JAN 16 | WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data                             |
|              |  |        |  |
| NEWS EXPRESS | NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006. |        |  |
|              |  |        |  |
| NEWS HOURS   | STN Operating Hours Plus Help Desk Availability  |        |  |
| NEWS LOGIN   | Welcome Banner and News Items  |        |  |
| NEWS IPC8    | For general information regarding STN implementation of IPC 8  |        |  |
| NEWS X25     | X.25 communication option no longer available  |        |  |

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 11:27:50 ON 19 JAN 2007

=> file reg

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SINCE FILE

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ENTRY

SESSION

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0.21

FILE 'REGISTRY' ENTERED AT 11:28:04 ON 19 JAN 2007

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STRUCTURE FILE UPDATES: 17 JAN 2007 HIGHEST RN 917745-84-7

DICTIONARY FILE UPDATES: 17 JAN 2007 HIGHEST RN 917745-84-7

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TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

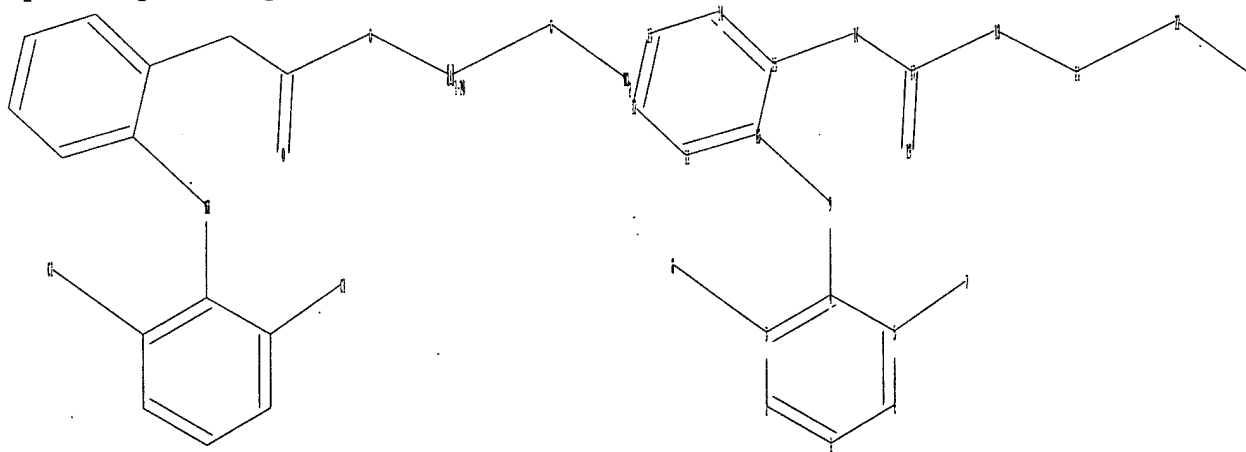
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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

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chain nodes :

7 8 9 16 17 18 19 21 22 23

ring nodes :

1 2 3 4 5 6 10 11 12 13 14 15

chain bonds :

3-8 4-9 5-7 9-10 15-16 16-17 17-18 17-19 18-21 21-22 22-23

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 10-11 10-15 11-12 12-13 13-14 14-15

exact/norm bonds :

4-9 9-10 17-18 17-19 18-21 21-22 22-23

exact bonds :

3-8 5-7 15-16 16-17

normalized bonds :

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G1:C,O

Match level :

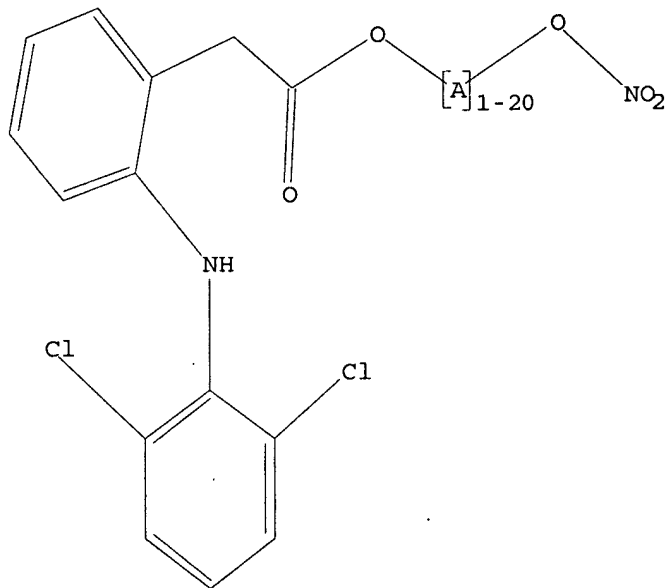
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:Atom  
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:CLASS 18:CLASS 19:CLASS  
21:CLASS 22:CLASS 23:CLASS

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS

L1 STR



G1 C,O

Structure attributes must be viewed using STN Express query preparation.

10527647.trn

Page 4

=> l1

SAMPLE SEARCH INITIATED 11:28:49 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 3 TO ITERATE

100.0% PROCESSED 3 ITERATIONS 3 ANSWERS  
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 3 TO 163  
PROJECTED ANSWERS: 3 TO 163

L2 3 SEA SSS SAM L1

=> l1 full

FULL SEARCH INITIATED 11:28:53 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 45 TO ITERATE

100.0% PROCESSED 45 ITERATIONS 14 ANSWERS  
SEARCH TIME: 00.00.01

L3 14 SEA SSS FUL L1

=> file medline caplus

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|----------------------|------------------|---------------|
| FULL ESTIMATED COST  | 172.55           | 172.76        |

FILE 'MEDLINE' ENTERED AT 11:29:28 ON 19 JAN 2007

FILE 'CAPLUS' ENTERED AT 11:29:28 ON 19 JAN 2007  
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=> l3

L4 41 L3

=> dup rem l4

PROCESSING COMPLETED FOR L4

L5 33 DUP REM L4 (8 DUPLICATES REMOVED)

=> d ibib abs hitstr 1-33

L5 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:191976 CAPLUS  
 DOCUMENT NUMBER: 144:273755  
 TITLE: Preparation of prodrugs containing novel biocleavable linkers  
 INVENTOR(S): Satyam, Apparao  
 PATENT ASSIGNEE(S): Nicholas Piramal India Ltd., India  
 SOURCE: U.S. Pat. Appl. Publ., 181 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.    | KIND | DATE     | APPLICATION NO. | DATE     |
|---------------|------|----------|-----------------|----------|
| US 2006046967 | A1   | 20060302 | US 2005-211396  | 20050826 |
| US 2006205674 | A2   | 20060914 |                 |          |
| WO 2006027711 | A2   | 20060316 | WO 2005-1852797 | 20050826 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, GU, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SV, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-604632P P 20040926  
 IN 2005-MU779 A 20050701

OTHER SOURCE(S): MARPAT 144:273755

AB The invention provides compds. D1-L1-E-A-B-A1-E-(L-E-A1-B-A-E)0-2-L2-D2  
 [B is a bond, (CH2)1-6, (CH2CH2O)1-1000, S-S, S-S:O, S-SO2 or S-S:NH; A, A1 are independently a bond, (CH2)1-8, 1,2-, 1,3- or 1,4-phenylene; D1 is a therapeutic agent having one or more functional groups OH, SH, NHRI,

CO2H, CONHRI, O2CNHRI, SO2NHRI, NR1CONHNHRI or NR1SO2NHRI (R1 is H, alkyl, aryl, etc.); D2 is D1, a peptide, protein, monoclonal antibody, vitamin, NO, NO2, NONOate, a nitric oxide-releasing group, a polymer, etc.; E is independently CH2 or a bond; L1, L2 are independently a bond, O, S, NHRI, L, or a linkage) or their pharmaceutically-acceptable salts  
 for use as prodrugs, including NO-releasing prodrugs. Thus, aspirin prodrug 2-AcOCH4CONHCH2CH2SSCH2CH2ONO2 was prepared and shown to release salicylate in rats in a sustained and controlled manner starting from 1 h through 12 h.  
 IT 877865-14-OP  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

L5 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1154582 CAPLUS  
 DOCUMENT NUMBER: 142:100367  
 TITLE: Pharmaceutical compositions based on diclofenac derivative  
 INVENTOR(S): Gustafsson, Christina; Kjellberg, Ulf; Morein, Sven  
 PATENT ASSIGNEE(S): Niccox S.A., Fr.  
 SOURCE: PCT Int. Appl., 26 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.    | KIND | DATE     | APPLICATION NO. | DATE     |
|---------------|------|----------|-----------------|----------|
| WO 2004112753 | A1   | 20041229 | WO 2004-SE1017  | 20040623 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, GU, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SV, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2529963 A1 20041229 CA 2004-2529963 20040623  
 EP 1635790 A1 20060322 EP 2004-749055 20040623

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

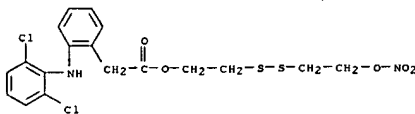
US 2006141044 A1 20060629 US 2005-560824 20051215  
 SE 2003-1880 A 20030625

PRIORITY APPLN. INFO.: WO 2004-SE1017 W 20040623

AB The present invention relates to particles comprising the NO-donating diclofenac derivative, 2-[(2-(nitrooxy)ethoxy)ethyl] 2-[(2,6-dichlorophenyl)amino]phenylacetate (I), optionally mixed with one or more surfactant(s) and to a new drug delivery composition comprising said particles optionally in combination with a second drug. Furthermore, the invention relates to processes for preparing said particles and drug delivery composition as well as the use of said composition in the manufacturing of a medicament. For example, 10.5 g I and 29.5 g Pearlitol 100 SD were mixed and the mixture was heated to 75° until the drug was fully melted. The mixture was cooled to room temperature and the powder obtained was sieved through a 0.355 mm sieve. The sieved powder (37.8 g) was mixed with 0.62 g microcryst. cellulose, 0.63 g Polyvidon XL and 0.41 g Polyvidon K-30, and the powder was wet-granulated. The granulate was dried overnight at 45°, 0.38 g colloidal silica was added and the powder was mixed. Sodium stearyl fumarate (0.20 g) was added to the mixture followed by mixing. The granulate was filled into hard gelatin capsules. The drug release from capsules was 12.1%, 33.4%, 60.7%, 79.6% and 88.14% in 5, 10, 20, 45, and

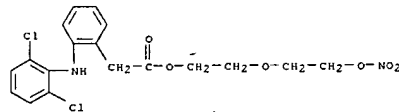
L5 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

(Uses)  
 (prepn. of prodrugs contg. novel biocleavable linkers)  
 RN 877865-14-0 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[(2-(nitrooxy)ethyl)dithio]ethyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

90 min, resp.  
 IT 174454-43-4  
 RI: PRP (Properties); THU (Therapeutic use); BIOL (Biological study);  
 USES  
 (Uses)  
 (porous particle compns. comprising NO-donating diclofenac derivative)  
 RN 174454-43-4 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[(2-(nitrooxy)ethoxy)ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:354783 CAPLUS  
 DOCUMENT NUMBER: 140:350593  
 TITLE: Use of NO-donating NSAIDs for the treatment of conditions associated with gastrointestinal motility  
 INVENTOR(S): Jonzon, Bror; Hoogstraate, Janet  
 PATENT ASSIGNEE(S): Astrazeneca UK Limited, UK  
 SOURCE: PCT Int. Appl., 34 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2004035042          | A1   | 20040429 | WO 2003-SE1603  | 20031015   |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, NG, TD, TG   |          |                 |            |
| AU 2003269774          | A1   | 20040504 | AU 2003-269774  | 20031015   |
| PRIORITY APPLN. INFO.: |  |          | SE 2002-3093    | A 20021018 |
|                        |  |          | WO 2003-SE1603  | W 20031015 |

OTHER SOURCE(S): MARPAT 140:350593  
 AB The invention discloses the use of NO-donating nonsteroidal antiinflammatory drugs in the treatment of conditions associated with gastrointestinal motility, a method of treatment of such conditions, and the use of pharmaceutical compns. comprising one or more NO-donating NSAID(s) in the treatment of such conditions. More particularly, the invention is directed to the use of one or more NO-donating NSAID(s) for the manufacture of a medicament for the treatment of conditions associated with disturbed gastrointestinal motility.  
 IT 156661-01-7  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (NO-donating NSAIDs for treatment of conditions associated with gastrointestinal motility)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

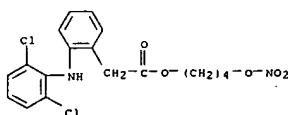
L5 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:267282 CAPLUS  
 DOCUMENT NUMBER: 140:287165  
 TITLE: Manufacturing process for NO-donating compounds such as NO-donating diclofenac  
 INVENTOR(S): Andersson, Johan; Belli, Aldo; Cannata, Vincenzo; Hedberg, Martin; Palmgren, Andreas; Schuldei, Sigrid; Stroem, Marika; Villa, Marco  
 PATENT ASSIGNEE(S): Astrazeneca UK Limited, UK; Astrazeneca AB  
 SOURCE: PCT Int. Appl., 68 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2004026808          | A1   | 20040401 | WO 2003-SE1465  | 20030918   |
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| CA 2498943             | A1   | 20040401 | CA 2003-2498943 | 20030918   |
| AU 2003265035          | A1   | 20040408 | AU 2003-265035  | 20030918   |
| BR 2003014365          | A  | 20050719 | BR 2003-14365   | 20030918   |
| EP 1558559             | A1   | 20050803 | EP 2003-797782  | 20030918   |
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| CN 1684940             | A  | 20051019 | CN 2003-822285  | 20030918   |
| JP 2006500409          | T  | 20060105 | JP 2004-538109  | 20030918   |
| ZA 200502224           | A  | 20060222 | ZA 2005-2224    | 20050316   |
| US 2006122402          | A1   | 20060608 | US 2005-527647  | 20050801   |
| PRIORITY APPLN. INFO.: |  |          | SE 2002-2801    | A 20020920 |
|                        |  |          | SE 2003-1476    | A 20030520 |
|                        |  |          | WO 2003-SE1465  | W 20030918 |

OTHER SOURCE(S): CASREACT 140:287165; MARPAT 140:287165  
 AB NO-donating compds. MlnAmCO2XONOp [M = residue of an NSAID, COX-1 inhibitor or COX-2 inhibitor; L = O, S, CO2, (un)substituted CONH, NH, CO, CH2, CH2CO, CH2CONH, CH2CO2; A = (un)substituted alkylene; X = carbon linker; m, n = 0-3; p = 1, 2] are prepared by treating MlnAmCO2H with HOXOH, treating MlnAmCO2XOH with RSOC1 [R = alkyl, (un)substituted Ph, CH2Ph, halogen, CF3, C4F9], and treating MlnAmCO2XO3SR with nitrate. A substantially crystalline form of 2-[(2-(nitrooxy)ethoxy)ethyl] (2-[(2,6-dichlorophenyl)amino]phenyl)acetate is reported.  
 IT 174454-43-4P  
 RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (manufacturing process for NO-donating compds. such as NO-donating

L5 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

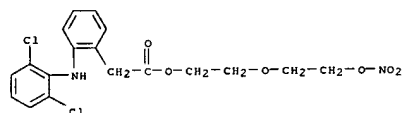


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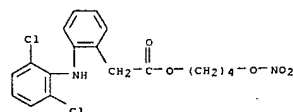
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L5 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

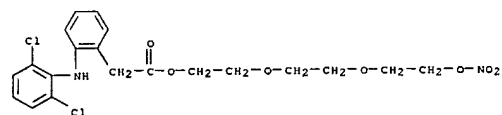
diclofenac)  
 RN 174454-43-4 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



IT 156661-01-7P 676125-87-4P  
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)  
 (manufacturing process for NO-donating compds. such as NO-donating diclofenac)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RN 676125-87-4 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethoxyethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:41217 CAPLUS

DOCUMENT NUMBER: 140:111135

TITLE: Preparation of nitrosated nonsteroidal antiinflammatory compounds

INVENTOR(S): Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; Garvey, David S.; Gaston, Ricky D.; Khanapure, Subhash P.; Letts, Gordon L.; Lin, Chia-En; Ranatunge, Ramani R.; Richardson, Stewart K.; Schroeder, Joseph D.; Stevenson, Cheri A.; Wey, Shioh-Jyi

PATENT ASSIGNEE(S): NitroMed, Inc., USA

SOURCE: PCT Int. Appl., 145 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

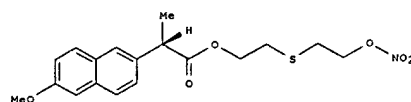
PATENT INFORMATION:

| PATENT NO.  | KIND | DATE      | APPLICATION NO. | DATE        |
|---|------|-----------|-----------------|-------------|
| WO 2004004648   | A2   | 20040115  | WO 2003-US21026 | 20030703    |
| WO 2004004648   | A3   | 200401028 |                 |             |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |      |           |                 |             |
| RW: GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  |      |           |                 |             |
| CA 2491127  | A1   | 20040115  | CA 2003-2491127 | 20030703    |
| AU 2003247792   | A1   | 20040123  | AU 2003-247792  | 20030703    |
| US 2004024057   | A1   | 20040205  | US 2003-612014  | 20030703    |
| US 7163958  | B2   | 20070116  |                 |             |
| EP 1539729  | A2   | 20050615  | EP 2003-763193  | 20030703    |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK   |      |           |                 |             |
| JP 2005539089   | T    | 20051222  | JP 2004-562619  | 20030703    |
| US 2005222243   | A1   | 20051006  | US 2005-134358  | 20050523    |
| PRIORITY APPLN. INFO.:  |      |           |                 |             |
|   |      |           | US 2002-393111P | P 20020703  |
|   |      |           | US 2002-397979P | P 20020724  |
|   |      |           | US 2002-418353P | P 20021016  |
|   |      |           | US 2003-449798P | P 20030226  |
|   |      |           | US 2003-456182P | P 20030321  |
|   |      |           | US 2003-612014  | A3 20030703 |
|   |      |           | WO 2003-US21026 | W 20030703  |

OTHER SOURCE(S): MARPAT 140:111135

L5 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

G1



II

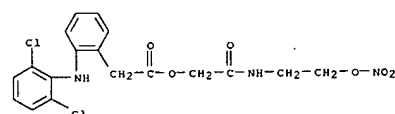
AB Title compds. RnRMC-CO-X [Rn = H, alkyl; Rn = 4-((thiophen-2-yl)carbonyl)phenyl, 3-(benzoyl)phenyl, etc.; X = Y-alkyl-aryl, etc.; Y = O, S; I] are prepared. For instance, naproxen is coupled to 2,2'-thiodiethanol (CH<sub>2</sub>Cl<sub>2</sub>, DNAP, EDCI) and treated with Ac<sub>2</sub>O/HNO<sub>3</sub> at 0° to give II. I are nitrosated nonsteroidal antiinflammatory drugs (NSAIDs) used alone or are combined with one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase. The invention provides methods for treating inflammation, pain, fever, gastrointestinal disorders, etc.

IT 183195-09-7P, [N-[(2-(Nitrooxy)ethyl)carbamoyl]methyl 2-[(2-(2,6-dichlorophenyl)amino)phenyl]acetate 646511-34-4P, (2S)-2,3-Bis(nitrooxy)propyl 2-[(2-[(2,6-dichlorophenyl)amino]phenyl]acetate 646511-36-6P, (2R)-2,3-Bis(nitrooxy)propyl 2-[(2-(2,6-dichlorophenyl)amino)phenyl]acetate (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

[Preparation of naproxen-derived nitrosated antiinflammatory compds.]

RN 183195-09-7 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[(2-(nitrooxy)ethylamino)-2-oxoethyl ester (9CI) (CA INDEX NAME)

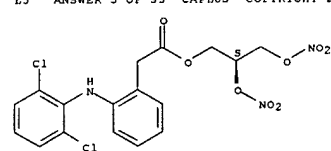


RN 646511-34-4 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, (2S)-2,3-bis(nitrooxy)propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

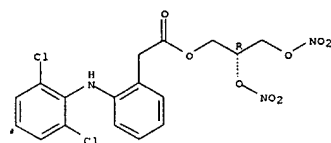
L5 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 646511-36-6 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, (2R)-2,3-bis(nitrooxy)propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:2666 CAPLUS

DOCUMENT NUMBER: 140:65191

TITLE: Oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability

INVENTOR(S): Del Soldato, Piero; Santus, Giancarlo; Macelloni, Cristina

PATENT ASSIGNEE(S): Nicox S.A., Fr.

SOURCE: PCT Int. Appl., 46 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

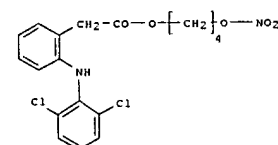
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE       |
|---|------|----------|-----------------|------------|
| WO 2004000273   | A1   | 20031231 | WO 2003-EP6496  | 20030620   |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |      |          |                 |            |
| RW: GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |            |
| IT 2002MI1392   | A1   | 20031229 | IT 2002-MI1392  | 20020625   |
| CA 2491152  | A1   | 20031231 | CA 2003-2491152 | 20030620   |
| AU 2003246564   | A1   | 20040106 | AU 2003-246564  | 20030620   |
| EP 1526839  | A1   | 20050504 | EP 2003-760660  | 20030620   |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK   |      |          |                 |            |
| CN 1665486  | A    | 20050907 | CN 2003-815181  | 20030620   |
| JP 2005530835   | T    | 20051013 | JP 2004-514802  | 20030620   |
| NZ 537204   | A    | 20060728 | NZ 2003-537204  | 20030620   |
| ZA 2004010109   | A    | 20050902 | ZA 2004-10109   | 20041214   |
| NO 200500347  | A    | 20050121 | NO 2005-347     | 20050121   |
| US 2006171969   | A1   | 20060803 | US 2005-515621  | 20050912   |
| PRIORITY APPLN. INFO.:  |      |          |                 |            |
|   |      |          | IT 2002-MI1392  | A 20020625 |
|   |      |          | WO 2003-EP6496  | W 20030620 |

G1



I

L5 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 AB The present invention relates to new pharmaceutical compns. for the administration of liquid drugs in solid oral forms, said compns.

comprising one or more active ingredients, one or more surface-active agents and optionally a co-surfactant and/or an absorption enhancer absorbed on a solid inert carrier. An emulsion was prepared containing 1 100,

Cremophor EL 50, Phospholipon 80H 50, Aerosil 200 100, and Explotab 100 g.

IT 156661-01-7 174454-43-4 311336-64-8

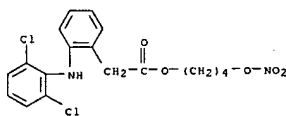
311336-66-0 639067-68-6

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (oral pharmaceutical liquid drugs containing nitrate ester NSAIDs

having improved bioavailability)

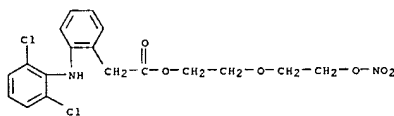
RN 156661-01-7 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RN 174454-43-4 CAPLUS

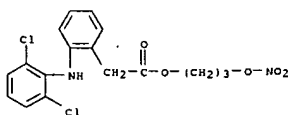
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



RN 311336-64-8 CAPLUS

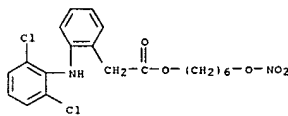
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 3-(nitrooxy)propyl ester (9CI) (CA INDEX NAME)

L5 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



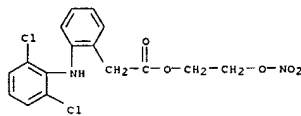
RN 311336-66-0 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 6-(nitrooxy)hexyl ester (9CI) (CA INDEX NAME)



RN 639067-68-8 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-(nitrooxy)ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2003:818296 CAPLUS  
 DOCUMENT NUMBER: 139:302040  
 TITLE: Nitrooxy derivatives of antiinflammatory/analgesic compounds for the treatment of arthritis  
 INVENTOR(S): Del Soldato, Piero  
 PATENT ASSIGNEE(S): Nicom S.A., Fr.  
 SOURCE: PCT Int. Appl., 71 pp.  
 CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2003084550          | A1   | 20031016 | WO 2003-EP3183  | 20030327   |
| W:                     | AE, AG, AL, AU, BA, BB, BR, BZ, CA, CN, CO, CR, CU, DM, DZ, EC, GE, GR, HR, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, SG, TH, TT, UA, US, UZ, VN, YU, ZA   |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG |          |                 |            |
| IT 2002MI0773          | A1   | 20031013 | IT 2002-MI773   | 20020411   |
| AU 2003224002          | A1   | 20031020 | AU 2003-224002  | 20030327   |
| EP 1492543             | A1   | 20050105 | EP 2003-720377  | 20030327   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK   |          |                 |            |
| JP 2005522472          | T  | 20050728 | JP 2003-581790  | 20030327   |
| US 2007010458          | A1   | 20070111 | US 2006-509675  | 20060913   |
| PRIORITY APPLN. INFO.: |  |          | IT 2002-MI773   | A 20020411 |
|                        |  |          | WO 2003-EP3183  | W 20030327 |

OTHER SOURCE(S): MARPAT 139:302040

AB Antiinflammatory and/or antiinflammatory/analgesic compds. having the formula A(B)b(C)cD-N(O)s [A contains radical of nonsteroidal antiinflammatory or nonsteroidal antiinflammatory/analgesic drug; B, C = bivalent linking group; s = 1, 2; b0, c0 = 0, 1 (with proviso)], and salts

thereof, are disclosed for use in the treatment of arthritis.

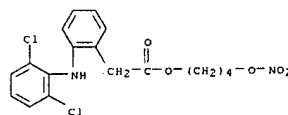
IT 156661-01-7 174454-43-4

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)

RN 156661-01-7 CAPLUS

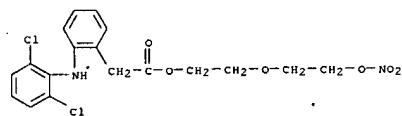
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

L5 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 174454-43-4 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT



L5 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:777566 CAPLUS

DOCUMENT NUMBER: 139:281272

TITLE: Nitric oxide-donating NSAIDS adsorbed into carrier particles

INVENTOR(S): Morein, Sven; Berg, Mats; Holmberg, Christina; Lundberg, Per Johan; Anders, Ringberg

PATENT ASSIGNEE(S): Astrazeneca Ab, Swed.; Astrazeneca Uk Limited

SOURCE: PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2003080029          | A1   | 20031002 | WO 2003-SE468   | 20031020   |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG   |          |                 |            |
| AU 2003216006          | A1   | 20031008 | AU 2003-216006  | 20031020   |
| EP 1490033             | A1   | 20041229 | EP 2003-745055  | 20031020   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK   |          |                 |            |
| US 2005129774          | A1   | 20050616 | US 2003-507368  | 20031020   |
| JP 2005533751          | T  | 20051110 | JP 2003-577859  | 20031020   |
| PRIORITY APPLN. INFO.: |  |          | SE 2002-895     | A 20020322 |
|                        |  |          | WO 2003-SE468   | W 20031020 |

AB The present invention relates to porous particles comprising NO-donating nonsteroidal anti-inflammatory compound optionally mixed with surfactants and to new solid drug delivery composition comprising the particles optionally

in combination with a second active drug. Furthermore, the invention relates to processes for producing the porous particles and solid drug delivery composition as well as the use of the composition in the manufacture of a medicament. The NO-donating NSAID may be in an oily or melted form. Thus, a tablet comprised 4-(nitrooxy)butyl (5)-2-(9-methoxy-2-naphthyl)propanoate (I) 250 and omeprazole 20 mg. Enteric over-coated pellets comprised omeprazole and a powder of the porous particles

containing I were manufactured sep. before compressing the 2 components.

IT 156661-01-7 174454-43-4

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (nitric oxide-donating NSAIDS adsorbed into carrier particles)

RN 156661-01-7 CAPLUS

L5 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:221490 CAPLUS

DOCUMENT NUMBER: 138:260440

TITLE: Self emulsifying drug delivery system containing NSAIDs

INVENTOR(S): Holmberg, Christina

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.

SOURCE: PCT Int. Appl., 49 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2003022249          | A1   | 20030320 | WO 2002-SE1598  | 20020905   |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG   |          |                 |            |
| EP 1427392             | A1   | 20040616 | EP 2002-765747  | 20020905   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK   |          |                 |            |
| JP 200504788           | T  | 20050217 | JP 2003-526379  | 20020905   |
| US 2004248974          | A1   | 20041209 | US 2004-488585  | 20040304   |
| PRIORITY APPLN. INFO.: |  |          | SE 2001-2993    | A 20010907 |
|                        |  |          | WO 2002-SE1598  | W 20020905 |

OTHER SOURCE(S): MARPAT 138:260440

AB A pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprises 1 or more NO-releasing NSAID(s), 1 or more

surfactants, of which at least one is phospholipid, the composition forming an in-situ oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise an addnl. oil or semi-solid fat.

Further, 1 or more short-chain alcs. can optionally be included in the composition. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and the proton pump inhibitor is enteric coated. Thus, a formulation contained Lipoid S100 0.30, propylene glycol 0.90, and a NO-releasing NSAID 4.00 g.

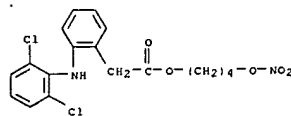
IT 156661-01-7 174454-43-4 311336-64-8

311336-66-0

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

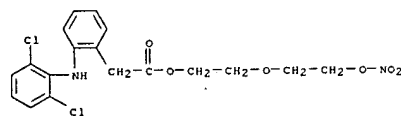
L5 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RN 174454-43-4 CAPLUS

CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

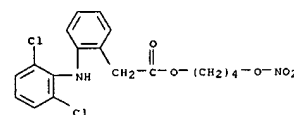
FORMAT

L5 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

(self emulsifying drug delivery system contg. NSAIDs)

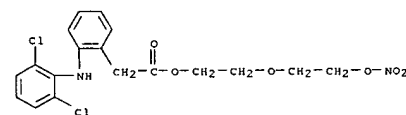
RN 156661-01-7 CAPLUS

CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



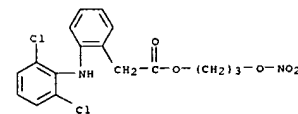
RN 174454-43-4 CAPLUS

CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



RN 311336-64-8 CAPLUS

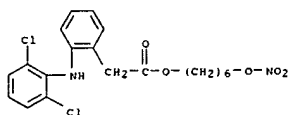
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 3-(nitrooxy)propyl ester (9CI) (CA INDEX NAME)



RN 311336-66-0 CAPLUS

CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 6-(nitrooxy)hexyl ester (9CI) (CA INDEX NAME)

L5 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

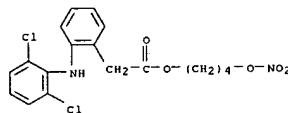
FORMAT

L5 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:133017 CAPLUS  
DOCUMENT NUMBER: 138:163547  
TITLE: Nitrooxy compounds for treatment of vasculopathies  
INVENTOR(S): Del Soldato, Piero  
PATENT ASSIGNEE(S): Nicox S.A., Fr.  
SOURCE: PCT Int. Appl., 26 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2003013499          | A2   | 20030220 | WO 2002-EP8374  | 20020726   |
| WO 2003013499          | A3   | 20031231 |                 |            |
| W:                     | AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GE, GR, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TH, TR, TT, UA, US, UZ, VN, YU, ZA             |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, ME, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG |          |                 |            |
| IT 2001MI1744          | A1   | 20030210 | IT 2001-MI1744  | 20010809   |
| AU 2002333276          | A1   | 20030224 | AU 2002-333276  | 20020726   |
| PRIORITY APPLN. INFO.: |  |          | IT 2001-MI1744  | A 20010809 |
|                        |  |          | WO 2002-EP8374  | W 20020726 |

OTHER SOURCE(S): MARPAT 138:163547  
AB The invention discloses the use for vasculopathy treatment of nitrooxy compds. (Markush included), or salts thereof. Compds. of the invention include e.g. 2-fluoro- $\alpha$ -methyl-4-diphenylacetic acid (4-nitrooxy)butyl ester (NO-flurbiprofen).  
IT 156661-01-7  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (nitrooxy compds. for treatment of vasculopathies)  
RN 156661-01-7 CAPLUS  
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

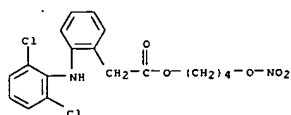
L5 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:736089 CAPLUS  
DOCUMENT NUMBER: 137:253012  
TITLE: Pharmaceutical compositions containing NO-releasing NSAID and surfactants  
INVENTOR(S): Siekmann, Britta; Thoring, Barbro  
PATENT ASSIGNEE(S): Astazeneca AB, Swed.  
SOURCE: PCT Int. Appl., 37 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

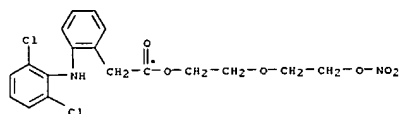
| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2002074282          | A1   | 20020926 | WO 2002-SE476   | 20020313   |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, LU, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG   |          |                 |            |
| CA 2435825             | A1   | 20020926 | CA 2002-2435825 | 20020313   |
| EP 1370239             | A1   | 20031217 | EP 2002-704035  | 20020313   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR   |          |                 |            |
| CN 1496253             | A  | 20040512 | CN 2002-806527  | 20020313   |
| BR 2002007760          | A  | 20040601 | BR 2002-7760    | 20020313   |
| JP 2004523577          | T  | 20040805 | JP 2002-572990  | 20020313   |
| ZA 2003006282          | A  | 20041123 | ZA 2003-6282    | 20030813   |
| US 2004056494          | A1   | 20040520 | US 2003-471178  | 20030909   |
| NO 2003004026          | A  | 20031111 | NO 2003-4026    | 20030911   |
| PRIORITY APPLN. INFO.: |  |          | SE 2001-901     | A 20010315 |
|                        |  |          | WO 2002-SE476   | W 20020313 |

OTHER SOURCE(S): MARPAT 137:253012  
AB A new pharmaceutical composition in the form of lipoglobules comprises (a) 1 or more NO-releasing NSAIDs; (b) 1 or more surfactants; and (c) an aqueous phase, and is useful for the treatment of pain and inflammation. Thus, a composition contained 4-(nitrooxy)butyl 6-methoxy- $\alpha$ -methyl-2-naphthaleneacetate 0.77, fractionated coconut oil 2.97, Phospholipon-80 0.76, and Poloxamer-407 1.61 mg/g.  
IT 156661-01-7 174454-43-4 311336-64-8  
311336-66-0  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmaceutical compns. containing NO-releasing NSAID and surfactants)  
RN 156661-01-7 CAPLUS  
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

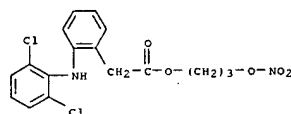
LS ANSWER 11 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



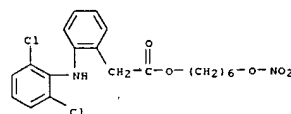
RN 174454-43-4 CAPLUS  
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



RN 311336-64-8 CAPLUS  
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 3-(nitrooxy)propyl ester (9CI) (CA INDEX NAME)



RN 311336-66-0 CAPLUS  
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 6-(nitrooxy)hexyl ester (9CI) (CA INDEX NAME)



|    |                         |   |                           |
|----|-------------------------|---|---------------------------|
| L5 | ANSWER 12 OF 33         | CAPLUS                                    | COPYRIGHT 2007 ACS ON STN |
|    | ACCESSION NUMBER:       | 2001:676579                               | CAPLUS                    |
|    | DOCUMENT NUMBER:        | 15:231708                                 |                           |
|    | TITLE:                  | New self emulsifying drug delivery system |                           |
|    | INVENTOR(S):            | Holmberg, Christina; Siekmann, Britta     |                           |
|    | PATENT APPLICANT(S):    | ASTRAZENECA AB, SWED                      |                           |
|    | SOURCE:                 | PCT Int. Appl., 56 pp.                    |                           |
|    |                         | CODEN: PIXXD2                             |                           |
|    | DOCUMENT TYPE:          | Patent                                    |                           |
|    | LANGUAGE:               | English                                   |                           |
|    | FAMILY ACC. NUM. COUNT: | 1   |                           |
|    | PATENT INFORMATIONS:    |   |                           |

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE       |
|---|------|----------|-----------------|------------|
| WO 2001066088   | A1   | 20010913 | WO 2001-SE4657  | 20010306   |
| W: AR, AG, AL, AM, AT, AU, AZ, BA, BG, BG, BR, BY, BZ, CA, CN, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MM, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW |      |          |                 |            |
| RW: GH, GM, KE, FI, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |            |
| CA 2401498  | A1   | 20010913 | CA 2001-2401498 | 20010306   |
| EP 1267832  | A1   | 20030102 | EP 2001-910305  | 20010306   |
| EP 1267832  | B1   | 20040602 |                 |            |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, HU, PL, SK, CY, BG, BG   |      |          |                 |            |
| BR 2001009014   | A    | 20030603 | BR 2001-9014    | 20010306   |
| JP 2003525894   | J    | 20030902 | JP 2001-564741  | 20010306   |
| HU 20030882   | A2   | 20030929 | HU 2003-882     | 20010306   |
| EE 200200500  | A    | 20040216 | EE 2002-500     | 20010306   |
| AT 268162   | T    | 20040615 | AT 2001-910305  | 20010306   |
| NZ 521009   | A    | 20040625 | NZ 2001-521009  | 20010306   |
| PT 1267832  | T    | 20040930 | PT 2001-910305  | 20010306   |
| SE 2220728  | T3   | 20041214 | SE 2001-910305  | 20010306   |
| RU 270675   | C2   | 20060227 | RU 2002-122744  | 20010306   |
| IN 2002M001102  | A    | 20050304 | IN 2002-M01102  | 20020816   |
| ZA 2002006740   | A    | 20031124 | ZA 2002-6740    | 20020822   |
| US 2003161846   | US   | 20030828 | US 2002-220791  | 20020905   |
| NO 2002004272   | N    | 20021105 | NO 2002-4272    | 20020906   |
| HK 1050632  | A1   | 20050318 | HK 2003-102781  | 20030416   |
| PRIORITY APPLN. INFO.:  |      |          | SE 2000-773     | A 20000308 |
|   |      |          | WO 2001-SE4657  | W 20010306 |

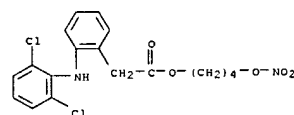
OTHER SOURCE(S): MARPAT 135:231708  
AB The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising: 1 or more NO-releasing NSAID(s), 1 or more surfactants, optionally an addnl. oil or semi-solid fat. The composition forms an instn oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise 1 or more short-chain alcs. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain

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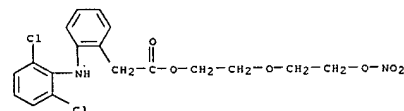
15 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

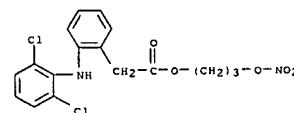
L5 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2007 ACS ON STN (Continued)  
and inflammation. Further within the scope of the invention is kit  
comprising a pharmaceutical compn. according to the invention in a unit  
dosage form, in combination with a proton pump inhibitor, and the proton  
pump inhibitor is enteric coated. Thus, a semisolid formulation  
contained  
a H<sub>2</sub>O-releasing NSAID 750, Pluronic F127 450, and omeprazole 20 g.  
IT 156661-01-7 17454-43-4 311336-64-8  
311336-66-0  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(self emulsifying drug delivery system)  
RN 156661-01-7 CAPLUS  
CN Benzenesulfonamide, 2-[(1,1,1-trichloro-4-(nitroxy)butyl  
amino)-3,3,3-trifluoropropyl]-, (CAS INDEX NAME)



RN 174454-43-4 CAPLUS  
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)

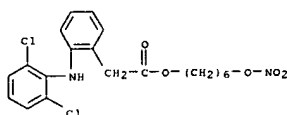


RN 311336-64-8 CAPLUS  
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 3-(nitrooxy)propyl  
ester (9CI) (CA INDEX NAME)



RN 311336-66-0 CAPLUS  
CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 6-(nitrooxy)hexyl ester (9CI) (CA INDEX NAME)

L5 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:137173 CAPLUS  
DOCUMENT NUMBER: 134:178396  
TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction  
INVENTOR(S): Del Soldato, Piero  
PATENT ASSIGNEE(S): Nicox S.A., Fr.  
SOURCE: PCT Int. Appl., 94 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

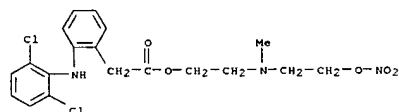
| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE        |
|------------------------|--|----------|-----------------|-------------|
| WO 2001012584          | A2   | 20010222 | WO 2000-EP7225  | 20000727    |
| WO 2001012584          | A3   | 20020829 |                 |             |
| W:                     | AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |             |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, T2, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |          |                 |             |
| CA 2381409             | A1   | 20010222 | CA 2000-2381409 | 20000727    |
| BR 2000013264          | A  | 20020416 | BR 2000-13264   | 20000727    |
| EP 1252133             | A2   | 20021030 | EP 2000-953102  | 20000727    |
| EP 1252133             | B1   | 20050608 |                 |             |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL   |          |                 |             |
| HU 200203539           | A2   | 20030328 | HU 2002-3939    | 20000727    |
| JP 2003515526          | T  | 20030507 | JP 2001-516885  | 20000727    |
| NZ 516889              | A  | 20041029 | NZ 2000-516889  | 20000727    |
| AU 781643              | B2   | 20050602 | AU 2000-65670   | 20000727    |
| AT 297375              | T  | 20050615 | AT 2000-953102  | 20000727    |
| EP 1593664             | A1   | 20051109 | EP 2005-104064  | 20000727    |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY   |          |                 |             |
| RU 2264383             | C2   | 20051120 | RU 2002-103509  | 20000727    |
| ES 2243292             | T3   | 20051201 | ES 2000-953102  | 20000727    |
| NZ 535559              | A  | 20051223 | NZ 2000-535559  | 20000727    |
| ZA 2002000628          | A  | 20030423 | ZA 2002-628     | 20020123    |
| NO 2002000623          | A  | 20020409 | NO 2002-623     | 20020208    |
| AU 2005202824          | A1   | 20050721 | AU 2005-202824  | 20050628    |
| PRIORITY APPLN. INFO.: |  |          | IT 1999-MI1817  | A 19990612  |
|                        |  |          | EP 2000-953102  | A3 20000727 |
|                        |  |          | WO 2000-EP7225  | W 20000727  |

OTHER SOURCE(S): MARPAT 134:178396  
AB Comps. or their salts of general formula (I): A-B-N(O)s wherein: a is an integer equal to 1 or 2; A = R-T1-, wherein R is the drug radical and T1 =

L5 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
(CO)t or (X)t', wherein X = O, S, NR1c, R1c is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -TB

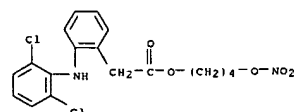
-X2-O- wherein TB = (CO) when t = 0, TB = X when t' = 0, X being as above defined; X2, bivalent radical, is such that the precursor drug of A and the precursor of B meet resp. the pharmacol. tests described in the description. Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT 326850-43-59  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)  
RN 326850-43-5 CAPLUS  
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[methyl(2-(nitrooxy)ethyl)amino]ethyl ester (9C1) (CA INDEX NAME)



L5 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

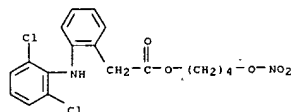
ACCESSION NUMBER: 2002:3642 CAPLUS  
DOCUMENT NUMBER: 137:179548  
TITLE: Synthesis and anti-inflammatory activity of benzenesulfonylfuroxan-coupled diclofenac  
AUTHOR(S): Li, Ruiwen; Zhang, Yihua; Ji, Hui; Yu, Xiaolin; Peng, Sixun  
CORPORATE SOURCE: Center of Drug Discovery, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China  
SOURCE: Yaoxue Xuebao (2001), 36(11), 821-826  
CODEN: YHHPAL; ISSN: 0513-4870  
Yaoxue Xuebao Bianjibu  
PUBLISHER: Journal  
DOCUMENT TYPE: Chinese  
LANGUAGE: Chinese  
AB New derivs. of diclofenac (DC) having activity of the parent drug and lacking its undesirable effects were screened by coupling DC with NO donor 3,4-dibenzesulfonylfuroxan through esterification and amidation, evaluating anti-inflammatory activity against xylene-induced mice ear swelling and carrageenan-induced rat paw edema, observing side effects in the rat gastrointestinal tract, and assessing NO releasing ability both in vitro and in vivo. Eleven new compds. 11-11 were synthesized, and their structures were determined by IR, 1HNMN, MS, and elemental anal. Compared with DC, 11-5 and 19 showed no significant difference in anti-inflammatory activity against xylene-induced mice ear swelling. 14 and 15 showed potency comparable to DC in treatment of carrageenan-induced rat paw edema. In GI tract, only slight mucosa surface erosion was found in both 14 and 15 treated rats, while deep ulcer was found in nitrofenac dosed rats and ulcer perforation was found in DC treated rats. Five of eleven rats treated with DC died, one of eight rats treated with nitrofenac died, but no death was found in eight rats dosed with 14 or 15. The detection of occult blood in feces and hemato. index also showed that the extent of GI tract bleeding in 14 and 15 treated rats was much less than that in both DC and nitrofenac treated rats. In addition, 14 and 15 released NO both in vitro and in vivo. Benzenesulfonylfuroxan-coupled DC may possess potency comparable to DC and less GI side effect than DC.  
IT 156661-01-7, Nitrofenac  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(synthesis and anti-inflammatory activity in mice of benzenesulfonylfuroxan-coupled diclofenac)  
RN 156661-01-7 CAPLUS  
CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9C1) (CA INDEX NAME)



L5 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L5 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:825952 CAPLUS  
 DOCUMENT NUMBER: 137:88271  
 TITLE: Pharmacological activity screening of furoxan-coupled diclofenac compounds  
 AUTHOR(S): Yu, Xiaolin; Ji, Hui; Zhang, Yihua; Li, Ruiwen; Peng, Sixun  
 CORPORATE SOURCE: Division of Pharmacology, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China  
 SOURCE: Zhongguo Yaokexue Xuebao (2001), 32(4), 301-305  
 CODEN: ZHYXES; ISSN: 1000-5048  
 PUBLISHER: Zhongguo Yaokexue  
 DOCUMENT TYPE: Journal  
 LANGUAGE: Chinese  
 AB The relationship in NO-non-steroidal anti-inflammatory drugs between anti-inflammatory activities, gastrointestinal (GI) side effects, and NO release was studied. Two screening models were used to determine the anti-inflammatory effects of the tested furoxan-coupled diclofenac compds.: one was xylene-induced mice ear swelling, and the other was carrageenan-induced rat paw edema. The effects of target compds. on rats' GI system were examined. The occult blood in feces was measured and some hematol. indexes (red blood cell count and Hb content) were also determined. The NO release in vitro and in vivo was determined. Anti-inflammatory activities were increased with the decrease of GI side effects. The GI side effects of all the target compds. with greater anti-inflammatory activities were less than diclofenac and nitrofenac, and NO release in vivo at 3 h was significantly increased. The results showed that the release of NO can resist GI side effects caused by NSAIDs.  
 IT 156661-01-7 Nitrofenac  
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmacol. activity screening of furoxan-coupled diclofenac compds.)  
 RN 156661-01-7 CAPLUS  
 CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

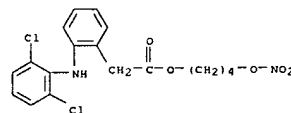
ACCESSION NUMBER: 2000:861483 CAPLUS  
 DOCUMENT NUMBER: 134:25340  
 TITLE: New use of compounds as antibacterial agents  
 INVENTOR(S): Eek, Arne; Raud, Johan  
 PATENT ASSIGNEE(S): AstraZeneca AB, Swed.  
 SOURCE: PCT Int. Appl., 45 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO.  | DATE        |
|---|------|----------|------------------|-------------|
| WO 2000072838   | A1   | 20001207 | WO 2000-SE1071   | 20000525    |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW |      |          |                  |             |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  |      |          |                  |             |
| TW 243672   | B    | 20051121 | TW 2000-89109689 | 20000519    |
| CA 2373653  | A1   | 20001207 | CA 2000-2373653  | 20000525    |
| BR 2000011116   | A    | 20020219 | BR 2000-11116    | 20000525    |
| EP 1196155  | A1   | 20020417 | EP 2000-937451   | 20000525    |
| EP 1196155  | B1   | 20040804 |                  |             |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO   |      |          |                  |             |
| TR 200103474  | T2   | 20020422 | TR 2001-3474     | 20000525    |
| HU 200201502  | A2   | 20020828 | HU 2002-1502     | 20000525    |
| JP 2003500442   | T    | 20030107 | JP 2003-500950   | 20000525    |
| EE 200100647  | A    | 20030217 | EE 2001-647      | 20000525    |
| NZ 515317   | A    | 20040528 | NZ 2000-515317   | 20000525    |
| AT 272396   | T    | 20040815 | AT 2000-937451   | 20000525    |
| AU 780678   | B2   | 20050407 | AU 2000-52623    | 20000525    |
| RU 2252032  | C2   | 20050520 | RU 2001-135826   | 20000525    |
| US 6593339  | B1   | 20030715 | US 2000-673007   | 20000929    |
| IN 2001MN01424  | A    | 20050304 | IN 2001-MN1424   | 20011115    |
| ZA 2001009497   | A    | 20010217 | ZA 2001-9497     | 20011116    |
| BG 106158   | A    | 20020628 | BG 2001-106158   | 20011128    |
| NO 2001005855   | A    | 20020130 | NO 2001-5855     | 20011130    |
| HK 1045814  | A1   | 20050401 | HK 2002-107373   | 20021009    |
| US 2004048917   | A1   | 20040311 | US 2003-426952   | 20030501    |
| PRIORITY APPLN. INFO.:  |      |          | SE 1999-2027     | A 19990601  |
|   |      |          | SE 1999-4704     | A 19991221  |
|   |      |          | WO 2000-SE1071   | W 20000525  |
|   |      |          | US 2000-673007   | A1 20000929 |

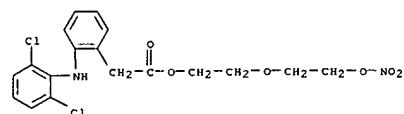
AB The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of

L5 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

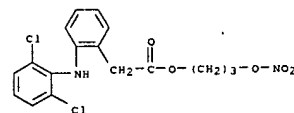
bacterial infections, esp. caused or mediated by Helicobacter pylori. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.  
 IT 156661-01-7 174454-43-4 311336-64-8  
 311336-66-0  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)  
 RN 156661-01-7 CAPLUS  
 CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RN 174454-43-4 CAPLUS  
 CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



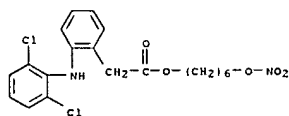
RN 311336-64-8 CAPLUS  
 CN Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, 3-(nitrooxy)propyl ester (9CI) (CA INDEX NAME)



RN 311336-66-0 CAPLUS

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L5 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 6-(nitrooxy)hexyl ester (9CI) (CA INDEX NAME)

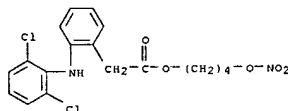


REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR  
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 RECORD. ALL CITATIONS AVAILABLE IN THE RE  
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L5 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:724578 CAPLUS  
 DOCUMENT NUMBER: 128:18496  
 TITLE: Study on paradoxical effects of NSAIDs on platelet activation  
 AUTHOR(S): Andrioli, Giuseppe; Lussignoli, Sabrina; Gai, Stefano; Benoni, Giuseppina; Bellavite, Paolo  
 CORPORATE SOURCE: Inst. Clinical Chem., Univ. Verona, Italy  
 SOURCE: Inflammation (New York) (1997), 21(5), 519-530  
 CODEN: INFLD4; ISSN: 0360-3997  
 PUBLISHER: Plenum  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB We recently described a stimulatory effect of high doses (>100 μmol/L) diclofenac on platelet adhesion. In this study we extend our research to the possible biochem. mechanisms of the observed effects, to other non steroidal anti-inflammatory drugs (NSAIDs) (flurbiprofen, indomethacin, acetylsalicylic acid, ibuprofen, nitrofenac and nitroflurbiprofen) and to the effect of high doses diclofenac and flurbiprofen on platelet aggregation. We observed that high doses of diclofenac and of flurbiprofen, but not of the other tested NSAIDs, increased platelet adhesion at doses ranging from 100 to 500 μmol/L, an effect completely removed by the 12-lipoxygenase inhibitor nordihydroguaiaretic acid. Moreover, they had no pro-aggregating effect, inhibiting platelet aggregation induced by 10 μmol/L arachidonic acid and dose-dependently increasing the [Ca<sup>2+</sup>]<sub>i</sub>. Finally, whereas no basal nitric oxide release by washed platelets was detected, when platelets were incubated by 500 μmol/L diclofenac or flurbiprofen, the production of nitric oxide, as measured by ams. of nitrite released, was 4.4 ± 0.5 and 3.8 ± 0.4 pmol/5 × 10<sup>8</sup> platelets/min. resp. Our data indicate that high doses diclofenac and flurbiprofen are promoters of the early phases of platelet activation, probably through the 12-lipoxygenase pathway.  
 IT 156661-01-7, Nitrofenac  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR  
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L5 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE  
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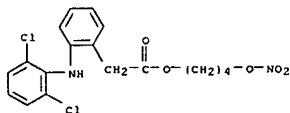
L5 ANSWER 18 OF 33 MEDLINE ON STN  
 ACCESSION NUMBER: 97132990 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8976349  
 TITLE: Nonsteroidal anti-inflammatory drug enteropathy in rats: role of permeability, bacteria, and enterohepatic circulation.  
 AUTHOR: Reuter B K; Davies N M; Wallace J L  
 CORPORATE SOURCE: Intestinal Disease Research Unit, Faculty of Medicine, University of Calgary, Alberta, Canada.  
 SOURCE: Gastroenterology, (1997 Jan) Vol. 112, No. 1, pp. 109-17.  
 Journal code: 0374630. ISSN: 0016-5085.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199701  
 ENTRY DATE: Entered STN: 19 Feb 1997  
 Last Updated on STN: 19 Feb 1997  
 Entered Medline: 21 Jan 1997

AB BACKGROUND & AIMS: The pathogenesis of nonsteroidal anti-inflammatory drug (NSAID)-induced small intestinal damage remains poorly understood. The aim of this study was to examine the relative importance of the three suggested components of the pathogenesis of NSAID enteropathy, namely, epithelial permeability, enteric bacterial numbers, and enterohepatic recirculation, using an NSAID derivative (nitrofenac) that does not cause small intestinal damage. METHODS: Rats were given diclofenac or nitrofenac at 12-hour intervals. Epithelial permeability to [51Cr]-ethylenediaminetetraacetic acid and enteric bacterial numbers were determined after 1-4 doses of the drugs. Serum levels and biliary excretion of the two drugs were determined by high-performance liquid chromatography. RESULTS: Diclofenac caused a progressive increase in epithelial permeability, marked increases in enteric gram-negative bacterial numbers, and frank intestinal ulceration. Nitrofenac caused similar changes in intestinal permeability after a single dose but no further increase with repeated administration. Moreover, nitrofenac had no effect on enteric bacterial numbers and did not cause frank ulceration. Unlike diclofenac, nitrofenac did not undergo extensive enterohepatic recirculation. Two other NSAIDs that do not undergo enterohepatic recirculation (nabumetone and aspirin) also did not modify enteric bacterial numbers or cause intestinal ulceration. CONCLUSIONS: Enterohepatic recirculation of NSAIDs is of paramount importance in the pathogenesis of enteropathy caused by these drugs, whereas suppression of prostaglandin synthesis is relatively unimportant.

L5 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1999:25752 CAPLUS  
 DOCUMENT NUMBER: 130:231736  
 TITLE: Nitric oxide as antimicrobial agent "in vivo"  
 AUTHOR(S): Cuzzolin, Laura; Adami, Alessandra; Crivellente, Federica; Benoni, Giuseppina  
 CORPORATE SOURCE: Institute of Pharmacology, University of Verona, Verona, Italy  
 SOURCE: Recent Research Developments in Antimicrobial Agents  
 CODEN: RDACFH  
 PUBLISHER: Research Signpost  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English  
 AB A review, with 28 refs. Since nitric oxide is recognized to possess antimicrobial properties and to be a critical mediator of gastrointestinal mucosal defense, in this review the authors report data about the "in vivo" effects of exogenous and endogenous nitric oxide on intestinal microflora and tissue integrity in healthy and inflamed rats. Initially, a model of chronic inflammation (adjuvant arthritis) was used to test the anti-inflammatory efficacy, the gastrointestinal tolerability and the effects on intestinal microflora of nitrofenac, a new NSAID-nitroderivative, in comparison to diclofenac; the results suggest similar therapeutic efficacy of both drugs, a better gastrointestinal tolerability for the new compound and no significant differences between the two drugs about the effects on intestinal microflora. Since it was not possible to correlate the gastrointestinal damage with the bacterial flora changes being the environment modified by the pathol., the role of exogenous nitric oxide, derived from the classical nitric oxide donor sodium nitroprusside, and of the endogenous one, induced by LPS administration, on intestinal flora and on tissue integrity, was investigated in healthy rats. Sodium nitroprusside did not induce any gastrointestinal damage and only partially affected bacterial growth; LPS resulted cytotoxic for all examined aerobic and anaerobic bacteria and induced a moderate jejunal damage. Sodium nitroprusside, when associated to LPS, reverted intestinal damage but not bacterial counts, while L-NAME completely prevented jejunal injury and partially recovered intestinal microflora: this suggest an involvement of an excessive local generation of nitric oxide formed by the inducible NOS enzyme. From this data, it appears evident that the effects of nitric oxide on intestinal bacteria and mucosa are strictly dependent on its concentration in the biol. micro-environment in which nitric oxide is released or present.  
 IT 156661-01-7, Nitrofenac  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (nitric oxide as in-vivo antimicrobial agent in intestine)

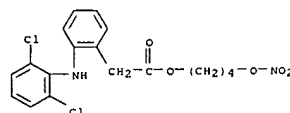
L5 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1998:63180 CAPLUS  
 DOCUMENT NUMBER: 128:176060  
 TITLE: NSAID-induced mucosal injury: Analysis of gastric toxicity of new-generation NSAIDs: ulcerogenicity compared with ulcer healing  
 AUTHOR(S): Halter, Fred; Rainsford, K. D.; Sirko, Steven P.; Schmassmann, Adrian  
 CORPORATE SOURCE: Gastrointestinal Unit, Inselspital, University Hospital, Bern, Switz.  
 SOURCE: Yale Journal of Biology and Medicine (1997), 70(1), 33-43  
 CODEN: YJBMAY; ISSN: 0044-0086  
 PUBLISHER: Yale Journal of Biology and Medicine  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Some nonsteroidal anti-inflammatory drugs (NSAIDs) delay healing of exptl. gastric ulcers. The 2 exptl. NSAIDs tebufelone and nitrofenac exert relatively low ulcerogenicity in various animal models compared with conventional NSAIDs. In addition, it has been reported that nitrofenac accelerates exptl. acute ulcer healing. The ulcerogenicity of tebufelone was compared with that of indomethacin in arthritic female Lewis rats in a single-dose and a 5-day dosage study. The interference of tebufelone and nitrofenac with ulcer healing was compared with that of indomethacin, diclofenac, omeprazole, and indomethacin plus omeprazole in Wistar rats with gastric cryo-ulcers. The rats were treated for 15 days and ulcer size was sequentially quantified by video endoscopy. Prostanoids in stomach and blood were assessed on day 15. The ulcerogenicity of tebufelone was markedly lower than that of indomethacin at doses with equipotent anti-inflammatory activities. Ulcer healing was accelerated by omeprazole in the 1st wk, but healing was delayed by tebufelone, nitrofenac, indomethacin and diclofenac during the 2nd wk. All the NSAIDs decreased prostanoid synthesis. Overall, tebufelone and nitrofenac delayed gastric ulcer healing to a similar extent as did conventional NSAIDs, even though tebufelone appeared to induce less mucosal damage when determined in standard ulcer assays in rats. Thus, there does not appear to be a relationship between the ulcerogenicity of these NSAIDs and their effect on ulcer healing.  
 IT 156661-01-7, Nitrofenac  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (ulcer formation and healing by)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

L5 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
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L5 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
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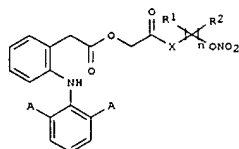
L5 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1996:681459 CAPLUS  
 DOCUMENT NUMBER: 125:328304  
 TITLE: Preparation of nitric esters of 2-(2,6-dihalophenylamino)phenylacetoxyacetic acid

derivatives  
 INVENTOR(S): Serra, Maria Xavier; Pi Sallent, Joan  
 PATENT ASSIGNEE(S): Prodes, S.A., Spain  
 SOURCE: Eur. Pat. Appl., 16 pp.  
 CODEN: EPXXDW

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

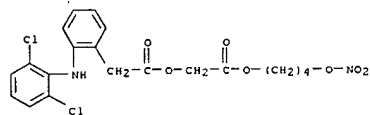
| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE       |
|---|------|----------|-----------------|------------|
| EP 738706   | A1   | 19961023 | EP 1996-106009  | 19960417   |
| EP 738706   | B1   | 19981007 |                 |            |
| R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE |      |          |                 |            |
| ES 2092962  | A1   | 19961201 | ES 1995-756     | 19950419   |
| ES 2092962  | B1   | 19970716 |                 |            |
| AU 9650428  | A    | 19961031 | AU 1996-50428   | 19960401   |
| AU 683790   | B2   | 19971120 |                 |            |
| ZA 9602981  | A    | 19961022 | ZA 1996-2981    | 19960415   |
| CA 2174287  | A1   | 19961020 | CA 1996-2174287 | 19960416   |
| HU 9600996  | A2   | 19961128 | HU 1996-996     | 19960417   |
| CN 1138027  | A    | 19961218 | CN 1996-105067  | 19960417   |
| AT 171936   | T    | 19981015 | AT 1996-106009  | 19960417   |
| NO 9601537  | A    | 19961021 | NO 1996-1537    | 19960418   |
| JP 09020738   | A    | 19970121 | JP 1996-98815   | 19960419   |
| US 5844696  | A    | 19961201 | US 1996-634763  | 19960419   |
| BR 9603235  | A    | 19960428 | BR 1996-3235    | 19960731   |
| PRIORITY APPL. INFO.:   |      |          | ES 1995-756     | A 19950419 |

OTHER SOURCE(S): CASREACT 125:328304; MARPAT 125:328304  
 GI

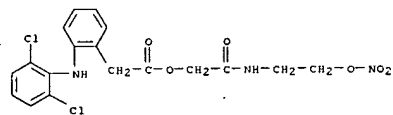


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L5 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 183195-09-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[(2-nitrooxy)ethylamino]-2-oxoethyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 AB The title compds. [I: A = F, Cl, Br; X = O, NH, NR (R = Cl-8 alkyl); R1, R2 = Cl-8 alkyl, n = 1-10], potentially useful as antiinflammatory agents (no data), were prepared by condensation of 2-(2,6-dihalophenylamino)phenylacetoxyacetic acid with a compound

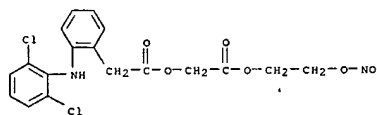
Y-(C)nR1R2ONO2 [Y = OH, NH2, NHR] in the presence of condensing agent such as N,N'-carbonyl diimidazole in an aprotic organic solvent.

IT 183195-04-2P 183195-06-4P 183195-07-5P  
 183195-09-7P  
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(Preparation of nitric esters of 2-(2,6-dihalophenylamino)phenylacetoxyacetic acid derivs.)

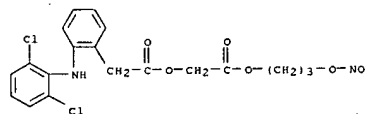
RN 183195-04-2 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[(2-nitrooxy)ethoxy]-2-oxoethyl ester (9CI) (CA INDEX NAME)



RN 183195-06-4 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[3-(nitrooxy)propoxy]-2-oxoethyl ester (9CI) (CA INDEX NAME)



RN 183195-07-5 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[4-(nitrooxy)butoxy]-2-oxoethyl ester (9CI) (CA INDEX NAME)

L5 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1996:253443 CAPLUS  
 DOCUMENT NUMBER: 124:332273

TITLE: Inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivatives with gastrointestinal-sparing properties  
 AUTHOR(S): Cirino, G.; Wheeler-Jones, C. P. D.; Wallace, J. L.; Del Soldato, P.; Baydoun, A. R.

CORPORATE SOURCE: Vascular Biology Research Centre, King's College, London, W8 7AH, UK  
 SOURCE: British Journal of Pharmacology (1996), 117(7), 1421-6  
 CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Stockton

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of novel nitric oxide-releasing nonsteroidal anti-inflammatory

compds. (NO-NSAIDs) on induction of nitric oxide (NO) synthase by bacterial lipopolysaccharide (LPS) were examined in a murine cultured macrophage cell line, J774. LPS-induced nitrite production was markedly attenuated by the nitroxybutyl ester derivs. of flurbiprofen (FNBE), aspirin, ketoprofen, diclofenac and ketorolac, with each compound

reducing accumulated nitrite levels by >40% at the maximum concns. (100 µg ml<sup>-1</sup>) used. Further examination revealed that nitrite production was

inhibited in a concentration-dependent (1-100 µg ml<sup>-1</sup>) manner by FNBE which at 100 µg ml<sup>-1</sup>

decreased LPS stimulated levels by 63.3±8.6% (n=7). The parent compound flurbiprofen was relatively ineffective over the same

concentration-range, inhibiting nitrite accumulation by 24±0.9% (n=3) at the maximum

concentration used (100 µg ml<sup>-1</sup>). FNBE reduced LPS-induced nitrite production when

added to cells up to 4 h after LPS. Thereafter, FNBE caused very little or no reduction in nitrite levels. Furthermore NO-NSAIDs (100 µg ml<sup>-1</sup>) did

not inhibit the metabolism of L-[3H]-arginine to citrulline by NO synthase isolated from LPS-activated macrophages. Western blot anal. demonstrated that NO synthase expression was markedly attenuated following co-incubation of J774 cell with LPS (1 µg ml<sup>-1</sup>; 24 h) and FNBE (100 µg ml<sup>-1</sup>; 24 h). Thus taken together, these findings indicate that NO-NSAIDs inhibit induction of NO synthase without directly affecting enzyme activity. In conclusion our results indicate that NO-NSAIDs can inhibit the inducible L-arginine-NO pathway, and are capable of suppressing NO synthesis by inhibiting expression of NO synthase. The clin. implications of these findings remain to be established.

IT 156661-01-7

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

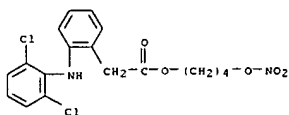
study, unclassified); BIOL (Biological study) (inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

RN 156661-01-7 CAPLUS

CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

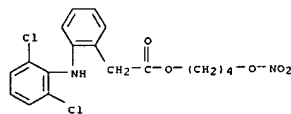


L5 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L5 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

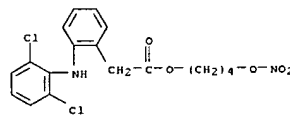
ACCESSION NUMBER: 1996:333513 CAPLUS  
 DOCUMENT NUMBER: 125:25397  
 TITLE: Nitric oxide-releasing NSAIDs, a novel class of safe and effective anti-inflammatory agents  
 AUTHOR(S): Del Soldato, P.; Cuzzolin, L.; Adami, A.; Conforti, A.; Crivellente, F.; Benoni, G.  
 CORPORATE SOURCE: Policlinico Borgo Roma, University of Verona, Verona, 37134, Italy  
 SOURCE: Inflammopharmacology (1996), 4(2), 181-188  
 CODEN: IAOAES; ISSN: 0925-4692  
 PUBLISHER: Kluwer  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English  
 AB A review with 19 refs. The pharmacotocol. profile were reported for three new nitro-anti-inflammatory agents, nitrofenac, nitronaproxen and nitroflurbiprofen with the following results: in models of acute (carrageenan edema) and chronic (adjuvant arthritis) inflammation in the rat, the nitro deriva., compared with the parent drugs, showed similar anti-inflammatory properties by significantly inhibiting both edema volume and arthritis development. The nitroso compds. showed markedly less ulcerogenic activity compared with the parent drugs both in acute conditions and at the end of the chronic inflammation test. The lack of gastrointestinal damage observed with these new anti-inflammatory drugs is the consequence of their ability to release NO. This hypothesis is supported by pharmacokinetic studies and a significant increase in nitrite/nitrate plasma levels.  
 IT 156661-01-7, Nitrofenac  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:258954 CAPLUS  
 DOCUMENT NUMBER: 124:332445  
 TITLE: Effects of a new class of NO-releasing NSAIDs on platelets and isolated arteries  
 AUTHOR(S): Minuz, P.; Lechi, C.; Bonaspace, S.; Gairo, S.; Adami, A.; Cuzzolin, L.; Del Soldato, P.; Benoni, G.  
 CORPORATE SOURCE: Istituto di Clinica Medica, University Verona, Italy  
 SOURCE: Inflammopharmacology (1996), 4(1), 83-90  
 CODEN: IAOAES; ISSN: 0925-4692  
 PUBLISHER: Kluwer  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB A new class of nitro deriva. of nonsteroidal anti-inflammatory drugs has recently been synthesized (Nicox Ltd., London, UK). In order to improve gastric tolerance of the parent compound, a side-chain, able to release nitric oxide, has been added to the core structure of the mol. We studied in vitro the effects of nitrofenac and two NO-aspirins (NCX 4215 and NCX 4016) on platelets and isolated arteries to identify any possible effect due to the release of nitric oxide or to the inhibition of cyclooxygenase activity. Nitrofenac induced a dose-dependent relaxation both with intact and (46% with 1 + 10-3 mol/L) and endothelium-denuded (75% with 1 + 10-3 mol/L) rings of rat aorta precontracted with epinephrine, while diclofenac did not affect this contraction (0% relaxation in intact and 22% in rubbed arteries). Pretreatment with diclofenac 1 + 10-3 mol/L significantly increased the vasorelaxant effects of nitrofenac at each drug concentration, both in intact (86% with 1 + 10-3 mol/L) and rubbed preps. (89%). NO-aspirins, unlike acetylsalicylic acid, were able to relax both intact and endothelium-denuded rings of rat aorta (100% relaxation). Methylene blue and oxyHb completely reversed the relaxation induced by nitrofenac and NO-aspirins, both in rubbed and intact aortic rings. Both NO-aspirins exhibited antiaggregating properties in arachidonic acid-stimulated human platelets, measured using a turbidimetric method (NCX 4215, 1 + 10-3 mol/L: 70% inhibition; NCX 4016, 1 + 10-4 mol/L: 100%). NCX 4016 proving as effective as acetylsalicylic acid 1 + 10-5 mol/L. Thrombin-induced platelet aggregation was inhibited in acetylsalicylic acid-treated platelets (NCX 4215, 1 + 10-3 mol/L: 50%, NCX 4016, 1 + 10-4 mol/L: 92%). NCX 4016 was also able to prevent thrombin-induced intracellular free calcium increase, an effect not observed with acetylsalicylic acid. In vitro thromboxane A2 production in human platelets, assayed by RIA as thromboxane B2 serum concentration, was reduced by NCX 4215, 1 + 10-3 mol/L (76%) and virtually abolished by NCX 4016 5 + 10-5 mol/L (95% inhibition). These results demonstrate in vitro the antiaggregating activity of NO-aspirins, NCX 4016 being more active than NCX 4215, and the vasorelaxant effects of all the tested mols. The mechanism involved is two-fold: release of nitric oxide and inhibition of cyclooxygenase.  
 IT 156661-01-7, Nitrofenac  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 RN 156661-01-7 CAPLUS  
 (NO-releasing NSAID effect on platelets and isolated arteries)

L5 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



10527647.trn

L5 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:163887 CAPLUS  
 DOCUMENT NUMBER: 124:201789  
 TITLE: Preparation of aryl nitrate ester compounds having antiinflammatory and well as analgesic and antithrombotic activities  
 INVENTOR(S): Del Soldato, Piero; Sanniccolo, Francesco  
 PATENT ASSIGNEE(S): Nicox Ltd., Ire.  
 SOURCE: PCT Int. Appl., 87 pp.  
 DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: English  
 PATENT INFORMATION: 2

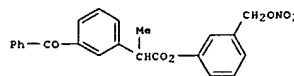
| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE        |
|---|------|----------|-----------------|-------------|
| WO 9530641  | A1   | 19951116 | WO 1995-EPI233  | 19950404    |
| W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN |      |          |                 |             |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG                |      |          |                 |             |
| CA 2190087  | C    | 19951116 | CA 1995-2190087 | 19950404    |
| CA 2190087  | A1   | 19951116 |                 |             |
| AU 9522156  | A    | 19951129 | AU 1995-22156   | 19950404    |
| AU 702662   | B2   | 19990225 |                 |             |
| EP 759899   | A1   | 19970305 | EP 1995-915185  | 19950404    |
| EP 759899   | B1   | 19990915 |                 |             |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE   |      |          |                 |             |
| HU 75961  | A2   | 19970528 | HU 1996-3107    | 19950404    |
| BR 9507634  | A    | 19970923 | BR 1995-7634    | 19950404    |
| JP 09512798   | T    | 19971222 | JP 1995-528615  | 19950404    |
| AT 184589   | T    | 19991015 | AT 1995-915185  | 19950404    |
| ES 2139199  | T3   | 20000201 | ES 1995-915185  | 19950404    |
| RU 2145595  | C1   | 20000220 | RU 1996-123280  | 19950404    |
| US 5861426  | A    | 19990119 | US 1997-737426  | 19970306    |
| US 5780495  | A    | 19980714 | US 1997-902570  | 19970729    |
| GR 3032078  | T3   | 20000331 | GR 1999-403169  | 19991208    |
| PRIORITY APPLN. INFO.:  |      |          | IT 1994-M1916   | A 19940510  |
|   |      |          | IT 1994-M11731  | A 19940809  |
|   |      |          | GB 1993-20599   | A 19931006  |
|   |      |          | WO 1995-EPI233  | W 19950404  |
|   |      |          | US 1996-624508  | A3 19960405 |

OTHER SOURCE(S): MARPAT 124:201789  
 G1

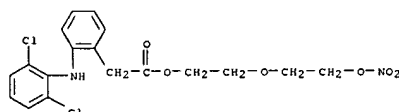
L5 ANSWER 26 OF 33 MEDLINE on STN  
 ACCESSION NUMBER: 95340109 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7615202  
 TITLE: A nitric oxide-releasing nonsteroidal anti-inflammatory drug accelerates gastric ulcer healing in rats.  
 AUTHOR: Elliott S N; McKnight W; Cirino G; Wallace J L  
 CORPORATE SOURCE: Intestinal Disease Research Unit, University of Calgary, Alberta, Canada.  
 SOURCE: Gastroenterology, (1995 Aug) Vol. 109, No. 2, pp. 524-30.  
 PUB. COUNTRY: Journal code: 0374630. ISSN: 0016-5085.  
 DOCUMENT TYPE: United States  
 LANGUAGE: Journal; Article; (JOURNAL ARTICLE)  
 FILE SEGMENT: English  
 ENTRY MONTH: Abridged Index Medicus Journals; Priority Journals  
 ENTRY DATE: 199508  
 Entered STN: 5 Sep 1995  
 Last Updated on STN: 5 Sep 1995  
 Entered Medline: 22 Aug 1995

AB BACKGROUND & AIMS: Nonsteroidal anti-inflammatory drugs (NSAIDs) have well-characterized inhibitory effects on gastric ulcer healing. A new class of gastrointestinal-sparing, nitric oxide-releasing NSAID derivatives has been recently described. This study was performed to determine if one of these compounds (nitrofenac) would influence healing of a preexisting ulcer. METHODS: Seven days after induction of gastric ulcer with serosal acetic acid, daily oral treatment with antiinflammatory doses of diclofenac, nitrofenac, or vehicle was started. After 7 days of treatment, the ulcer area was measured. The effects of misoprostol and two drugs that show in vitro selectivity for inhibiting cyclooxygenase 2 (nabumetone and L745,337) were also assessed. RESULTS: Diclofenac, nabumetone, and L745,337 had no effect on ulcer healing when compared with vehicle. Only diclofenac significantly decreased hematocrit and weight gain. On the other hand, nitrofenac significantly accelerated healing. Glycerol trinitrate also significantly and dose dependently accelerated healing. Nitrofenac suppressed cyclooxygenase 1 activity to a similar extent as diclofenac. CONCLUSIONS: These results show that an NO-releasing NSAID derivative and an NO donor could accelerate ulcer healing, whereas a standard NSAID, misoprostol, and two inhibitors of cyclooxygenase 2 had no effect. In addition to sparing the gastrointestinal tract, NO-releasing NSAIDs, despite suppressing cyclooxygenase activity, are capable of accelerating tissue repair.

L5 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



AB The title compds. AX(INO2 [A = R(COXu)t; t = 0, 1; u = 0, 1; X = O, (un)substituted NH or NRic wherein Ric = alkyl; R = (un)substituted Ph, etc.; X = YO; Y = alkylene, cycloalkylene, oxyalkyl, etc.] (e.g., I), which inhibit cyclooxygenase, are prepared  
 IT 174454-43-4p  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 and well as analgesic and antithrombotic activities)  
 RN 174454-43-4 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 2-[2-(nitrooxy)ethoxy]ethyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 27 OF 33 MEDLINE on STN  
 ACCESSION NUMBER: 95335361 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7610982  
 TITLE: Nitric oxide-releasing NSAIDs: a novel class of GI-sparing anti-inflammatory drugs.  
 AUTHOR: Wallace J L; Pittman Q J; Cirino G  
 CORPORATE SOURCE: Department of Pharmacology & Therapeutics, University of Calgary, Alberta, Canada.  
 SOURCE: Agents and actions. Supplements, (1995) Vol. 46, pp. 121-9.  
 PUB. COUNTRY: Journal code: 7801014. ISSN: 0379-0363.  
 DOCUMENT TYPE: Switzerland  
 LANGUAGE: Journal; Article; (JOURNAL ARTICLE)  
 FILE SEGMENT: English  
 ENTRY MONTH: Priority Journals  
 ENTRY DATE: 199508  
 Entered STN: 28 Aug 1995  
 Last Updated on STN: 28 Aug 1995  
 Entered Medline: 17 Aug 1995

AB The addition of a nitric oxide-releasing moiety to a number of common nonsteroidal anti-inflammatory drugs markedly reduces their toxicity in the gastrointestinal tract without interfering with their ability to inhibit prostaglandin synthesis. Moreover, the anti-inflammatory and anti-pyretic activities of the nitric-oxide releasing NSAID were comparable to the parent compound, while the anti-thrombotic activity in vivo was significantly enhanced. Nitric oxide-releasing NSAIDs may represent an alternative to existing anti-inflammatory, anti-pyretic and anti-thrombotic agents with greatly reduced toxicity in the gastrointestinal tract.

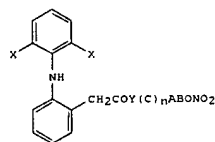
L5 ANSWER 28 OF 33 MEDLINE on STN DUPLICATE 4  
 ACCESSION NUMBER: 95230523 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7714752  
 TITLE: Plasma concentrations and pharmacokinetic parameters of nitrofenac using a simple and sensitive HPLC method.  
 AUTHOR: Benoni G; Terzi M; Adami A; Grigolini L; Del Soldato P; Curzolin L  
 CORPORATE SOURCE: Institute of Pharmacology, University of Verona, Policlinico Borgo Roma, Italy.  
 SOURCE: Journal of pharmaceutical sciences, (1995 Jan) Vol. 84, No. 1, pp. 93-5.  
 Journal code: 2985195R. ISSN: 0022-3549.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199505  
 ENTRY DATE: Entered STN: 24 May 1995  
 Last Updated on STN: 24 May 1995  
 Entered Medline: 18 May 1995

AB An accurate and sensitive HPLC method has been developed for the determination of nitrofenac, a new, original diclofenac derivate showing  
 a good tolerability and a wide anti-inflammatory profile, diclofenac, and its metabolites in plasma. This method has been applied to evaluate the pharmacokinetic parameters of the drugs, using a noncompartmental model, after the oral administration of 5 mg/kg nitrofenac to rats. Nitrofenac and the internal standard flufenamic acid were dissolved in acetonitrile, and diclofenac was dissolved in methanol. The drugs were eluted from a 5 microns LC-8 column with a mobile phase consisting of acetonitrile/water (50/50 v/v) adjusted to pH 3.3 with glacial acetic acid, at a flow rate  
 of 2 mL/min with UV detection at 280 nm for diclofenac and 275 nm for nitrofenac. The detection limit for the drugs in plasma was 25 ng/mL. The peak concentration of nitrofenac was reached 7 h after drug administration, while with diclofenac we observed three peaks at 2, 5, and  
 10 h; the mean residence time and the elimination rate constant for nitrofenac were 6.18 +/- 0.09 h and 0.37 +/- 0.03 h<sup>-1</sup> respectively, while those for diclofenac were 12.24 +/- 0.11 h and 0.11 +/- 0.04 h<sup>-1</sup>. Under our conditions, the metabolism of nitrofenac produced 21% diclofenac and other metabolites: the plasma concentrations and kinetic characteristics of diclofenac are enough to induce an anti-inflammatory activity, while the clinical importance of the other metabolites remains to be elucidated.

L5 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1994:508221 CAPLUS  
 DOCUMENT NUMBER: 121:108221  
 TITLE: Nitric esters of derivatives of 2-(2,6-di-halophenylamino)phenylacetic acid and process for their preparation  
 INVENTOR(S): Matji, Jose Antonio; Alcaide, Antonio  
 PATENT ASSIGNEE(S): Corlay S. L., Spain; Metgrove Ltd.  
 SOURCE: PCT Int. Appl., 28 pp.  
 CODEN: PIXX02  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

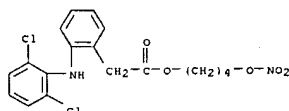
| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE       |
|--|------|----------|-----------------|------------|
| WO 9404484   | A1   | 19940303 | WO 1993-EP1906  | 19930720   |
| W: BR, CA, JP, KR, RU, UA, US                                      |      |          |                 |            |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |      |          |                 |            |
| EP 609415  | A1   | 19940810 | EP 1993-917596  | 19930720   |
| EP 609415  | B1   | 19961009 |                 |            |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE  |      |          |                 |            |
| JP 07500355  | T    | 19950112 | JP 1993-505826  | 19930720   |
| AT 143941  | T    | 19961015 | AT 1993-917596  | 19930720   |
| ES 2093979   | T3   | 19970101 | ES 1993-917596  | 19930720   |
| RU 2109009   | C1   | 19980420 | RU 1994-46148   | 19930720   |
| JP 3231042   | B2   | 20011119 | JP 1994-505826  | 19930720   |
| CA 2120942   | C    | 20050927 | CA 1993-2120942 | 19930720   |
| US 5597847   | A    | 19970128 | US 1994-211447  | 19940331   |
| PRIORITY APPLN. INFO.:   |      |          | IT 1992-MI2006  | A 19920820 |
|  |      |          | WO 1993-EP1906  | W 19930720 |

OTHER SOURCE(S): CASREACT 121:108221; MARPAT 121:108221  
 GI



AB Title compds. I (A, B = H, alkyl; X Br, Cl; Y = O, HN, R1N wherein R1 = alkyl; n = 1-10) useful as analgesics and antiinflammatories, and for treatment of immunol. disorders, cardiovascular, myocardial and brain

L5 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 ischemia and arterial thrombosis (data given for the 1st 2 disorders).  
 are prepd. by a process consisting of a limited no. of phases, satisfactory yields and high amts. even on an industrial basis. Br(CH2)4Cl in DMF was added to Na 2-[(2,6-dichlorophenyl)amino]phenylacetate in DMF to give the 4-chlorobutyl ester which was treated with AgNO3 in MeCN to give I (A = B = H, X = Cl, Y = O, n = 4). Analgesic and antiinflammatory activities  
 for I were shown.  
 IT 156661-01-7P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of, as analgesic and antiinflammatory)  
 RN 156661-01-7 CAPLUS  
 CN Benzenecetic acid, 2-[(2,6-dichlorophenyl)amino]-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 30 OF 33 MEDLINE on STN DUPLICATE 5  
 ACCESSION NUMBER: 9437444 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8088345  
 TITLE: A diclofenac derivative without ulcerogenic properties.  
 AUTHOR: Wallace J L; Reuter B; Cicala C; McKnight W; Grisham M; Cirino G  
 CORPORATE SOURCE: Gastrointestinal Research Group, Faculty of Medicine, University of Calgary, Alberta, Canada.  
 SOURCE: European journal of pharmacology, (1994 May 23) Vol. 257, No. 3, pp. 249-55.  
 Journal code: 1254354. ISSN: 0014-2999.  
 PUB. COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199410  
 ENTRY DATE: Entered STN: 31 Oct 1994  
 Last Updated on STN: 29 Jan 1996  
 Entered Medline: 18 Oct 1994

AB In this study, we assessed the effects of addition of a nitroxybutyl moiety to diclofenac on its ulcerogenic properties. The diclofenac derivative, 'nitrofenac', was examined in terms of its ability to induce acute gastric erosions and chronic-type gastric ulcers in rats and rabbits, respectively. The effects of these compounds on prostaglandin synthesis in the stomach and at a site of peripheral inflammation were also assessed, as were their anti-inflammatory properties in a model of acute inflammation. Diclofenac dose-dependently caused acute gastric mucosal injury in the rat at all doses tested (10-40 mg/kg), that was significantly greater in severity than that observed with the same doses of nitrofenac. In rabbits, twice-daily administration of diclofenac induced penetrating antral ulcers and small intestinal damage. No damage was observed in the stomach or small intestine of rabbits receiving nitrofenac. Diclofenac and nitrofenac exerted similar inhibitory effects on prostaglandin E2 synthesis in the stomach and in a carrageenan-sponge model of peripheral inflammation. These compounds exerted similar inhibitory effects on carrageenan-induced paw edema. Nitrofenac, but not diclofenac, caused a significant increase in plasma levels of nitrate/nitrite. These results suggest that the addition of a nitroxybutyl moiety to diclofenac markedly reduces the ulcerogenic properties of this compound without interfering with its ability to inhibit cyclo-oxygenase activity or to reduce acute inflammation.

L5 ANSWER 31 OF 33 MEDLINE on STN DUPLICATE 6  
 ACCESSION NUMBER: 94261529 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8202446  
 TITLE: Effects on intestinal microflora, gastrointestinal tolerability and antiinflammatory efficacy of diclofenac and nitrofenac in adjuvant arthritic rats.  
 AUTHOR: Cuzzolin L; Conforti A; Donini M; Adami A; Del Soldato P; Benoni G  
 CORPORATE SOURCE: Institute of Pharmacology, University of Verona, Italy.  
 SOURCE: Pharmacological research : the official journal of the Italian Pharmacological Society, (1994 Jan-Feb) Vol. 29, No. 1, pp. 89-97.  
 Journal code: 8907422. ISSN: 1043-6618.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article: (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199407  
 ENTRY DATE: Entered STN: 14 Jul 1994  
 Last Updated on STN: 29 Jan 1996  
 Entered Medline: 7 Jul 1994

AB Since it is known that nitric oxide plays an important protective role in maintaining the tissue integrity and is cytotoxic for invasive micro-organisms, diclofenac and a new original diclofenac-derivate, nitrofenac (containing the nitric oxide group), was administered at doses of 0.3 and 3 mg kg-1 per os to adjuvant arthritic rats. At the 14th, 21st and 28th days after arthritis induction, the antiinflammatory efficacy and the effects on intestinal microflora of the two drugs were evaluated; moreover, at the end of the study period, the gastrointestinal tract was examined macroscopically for any presence of lesions. Daily oral administration of diclofenac and nitrofenac at 3 mg kg-1 markedly and significantly inhibited arthritis development until the end of the study period. Some significant changes were observed in anaerobic and Gram-negative bacterial flora, particularly the total disappearance, in all treated rats, of *Escherichia coli* 1, also 7 days after the last drug administration. Finally, no ulcers or severe damage were observed macroscopically with either drug, even if some alterations in the mucosa and haemorrhagic effusions were more evident in rats treated with diclofenac at 3 mg kg-1. In conclusion, in this chronic model a similar therapeutic efficacy of diclofenac and nitrofenac is shown in arthritic rats. The better gastrointestinal tolerability observed in nitrofenac-treated rats could be attributed to the release of nitric oxide.

L5 ANSWER 32 OF 33 MEDLINE on STN DUPLICATE 7  
 ACCESSION NUMBER: 94285693 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8015340  
 TITLE: Markedly reduced intestinal toxicity of a diclofenac derivative.  
 AUTHOR: Reuter B K; Cirino G; Wallace J L  
 CORPORATE SOURCE: Gastrointestinal Research Group, University of Calgary, Alberta, Canada.  
 SOURCE: Life sciences, (1994) Vol. 55, No. 1, pp. PL1-8.  
 Journal code: 0375521. ISSN: 0024-3205.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article: (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199407  
 ENTRY DATE: Entered STN: 10 Aug 1994  
 Last Updated on STN: 29 Jan 1996  
 Entered Medline: 25 Jul 1994

AB Addition of a nitroxybutyl moiety to diclofenac greatly reduces its damaging effects on the gastric mucosa without altering its ability to suppress prostaglandin synthesis and exert anti-inflammatory actions.

The present study was performed in order to determine if this derivative of diclofenac, called nitrofenac, would also have less toxicity in the small and large intestine when administered repeatedly over a 1-2 week period. Healthy rats were given equimolar doses of diclofenac (10 mg/kg) or nitrofenac (15 mg/kg) twice daily for up to two weeks. All 10 rats receiving diclofenac died prior to completion of the study, exhibiting massive small intestinal ulceration and perforation. No deaths were observed in the rats treated with nitrofenac, and the only small intestinal abnormality observed was diffuse hyperemia. As nonsteroidal anti-inflammatory drugs have been shown to exacerbate colitis, we compared the effects of twice daily treatment with diclofenac (1-10 mg/kg) or nitrofenac (1.5-15 mg/kg) for 1 week in rats in which colitis had been induced with trinitrobenzene sulfonic acid. Diclofenac administration resulted in mortality which increased dose-dependently (e.g. 86% at 5 mg/kg) and was associated with perforation of the colon. Mortality was not observed with nitrofenac at doses of 1.5 or 7.5 mg/kg, while at 15 mg/kg the mortality rate was 33%. None of the doses of nitrofenac significantly augmented colonic injury or granulocyte infiltration (measured by myeloperoxidase activity). Suppression of colonic prostaglandin E2 synthesis was comparable with equimolar doses of diclofenac and nitrofenac. These studies demonstrate that nitrofenac has markedly reduced intestinal toxicity in healthy and colitic rats when compared to diclofenac.

L5 ANSWER 33 OF 33 MEDLINE on STN DUPLICATE 8  
 ACCESSION NUMBER: 94295465 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8023740  
 TITLE: Acute anti-inflammatory activity and gastrointestinal tolerability of diclofenac and nitrofenac.  
 AUTHOR: Conforti A; Donini M; Brocco G; Del Soldato P; Benoni G; Cuzzolin L  
 CORPORATE SOURCE: Institute of Pharmacology, University of Verona, Italy.  
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AB Diclofenac and its derivative nitrofenac were compared to test their anti-inflammatory efficacy and gastrointestinal toxicity in rats. A similar good anti-inflammatory activity of the two drugs was observed in carrageenan oedema and a marked gastrointestinal toxicity was induced by diclofenac, while nitrofenac failed to produce gastric damage even with very high doses (50 and 100 mg/kg). The lack of the gastric ulcers in rats treated with nitrofenac could be due to the absorption of the drug as an inactive inhibitor of PG synthesis and/or to the fact that probably nitric oxide is released in the intestine and plays an important protective role in maintaining the tissue integrity.

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SINCE FILE

TOTAL

ENTRY

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SINCE FILE

TOTAL

ENTRY

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